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<b>(51) International Patent Classification <sup>6</sup> :</b> <b>A61K 45/06</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 99/47171</b> <b>(43) International Publication Date:</b> 23 September 1999 (23.09.99)
<b>(21) International Application Number:</b> PCT/GB99/00801 <b>(22) International Filing Date:</b> 16 March 1999 (16.03.99)  <b>(30) Priority Data:</b> 9805557.7                      16 March 1998 (16.03.98)                      GB  <b>(71) Applicant (for all designated States except US):</b> MERCK SHARP & DOHME LIMITED [GB/GB]; Hertford Road, Hoddesdon, Hertfordshire EN11 9BU (GB).  <b>(72) Inventor; and</b> <b>(75) Inventor/Applicant (for US only):</b> DAWSON, Gerard, Raphael [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).  <b>(74) Agent:</b> HORGAN, James; Merck & Co., Inc., European Patent Dept., Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).		<b>(81) Designated States:</b> AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> COMBINATION OF A GABA-A ALPHA 5 INVERSE AGONIST AND A MUSCARINIC AGONIST		
<b>(57) Abstract</b>  The present invention relates to a combination of a muscarinic agonist and an inverse agonist of the GABA <sub>A</sub> α <sub>5</sub> receptor subtype, and the use of the combination in treating neurodegenerative conditions such as Alzheimer's Disease.		

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**COMBINATION OF A GABA-A ALPHA 5 INVERSE AGONIST AND  
A MUSCARINIC AGONIST**

The present invention relates to a combination of an muscarinic agonist  
5 and an inverse agonist of the GABA<sub>A</sub>  $\alpha_5$  receptor subtype, and the use of  
the combination in treating neurodegenerative conditions such as  
Alzheimer's Disease.

Alzheimer's Disease is a poorly understood neurodegenerative  
condition mainly affecting the elderly but also younger people who are  
10 generally genetically predispositioned to it.

One postulated method of treatment comprises the administration  
of muscarinic agonists which act on the cholinergic system. However this  
method suffers from the disadvantages that these compounds induce a  
range of side-effects including diarrhoea, salivation and nausea.

15 The present invention provides a new and surprisingly effective  
synergistic combination of an muscarinic agonist and an inverse agonist of  
the GABA<sub>A</sub>  $\alpha_5$  receptor subtype for separate, sequential or simultaneous  
administration.

The present invention provides a greater than expected  
20 improvement in the condition of subjects suffering from a  
neurodegenerative with an associated cognitive deficit, such as  
Alzheimer's Disease or Parkinson's disease, or from a cognitive deficit  
which may arise from a normal process such as aging or from an abnormal  
process such as injury, than would be expected from administration of the  
25 active ingredients alone. Further, the combination allows for a lower  
overall dose of each of the active ingredients to be administered thus  
reducing side effects and decreasing any reduction in the effectiveness of  
each of the active ingredients over time.

Muscarinic agonists which may be used include any which are  
30 known to the skilled person. Examples are methacholine and its chloride,  
carbachol, bethanechol, arecholine, pilocarpine, muscarine, McN-A-343,

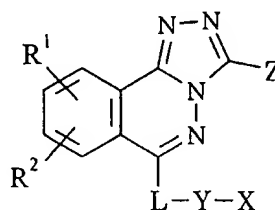
oxotremorine, milameline, xanomeline, cis-methyldioxalane, pirenzepine, gallamine, SB 202026, AF102B, AFDX 116 and RS-86.

Any inverse agonist of the GABA<sub>A</sub>  $\alpha_5$  receptor subtype may be used which fulfills the criteria of WO-A-9625948. The inverse agonist may be either binding selective for the  $\alpha_5$  subtype or functionally selective, or both. Thus the inverse agonist is preferably an antagonist, or has insignificant agonist or inverse agonist properties at the other GABA<sub>A</sub>  $\alpha$  receptor subtypes when measured in oocytes as described in WO-A-9625948.

Thus the inverse agonist preferably has a functional efficacy at the  $\alpha_5$  receptor subunit of less than -20% and functional efficacies at the  $\alpha_1$ ,  $\alpha_2$ , and  $\alpha_3$  receptor subunits of between -20 and +20%. By functional efficacy is meant the percentage modulation of the EC<sub>20</sub> response produced by GABA, upon coadministration of the inverse agonist, in oocytes expressing GABA<sub>A</sub> receptor channels containing the  $\alpha$  receptor subunit under test. Details of this measurement are given in WO-A-9625948.

The inverse agonist preferably binds selectively to GABA<sub>A</sub> receptors containing the  $\alpha_5$  subunit 10, 25 and particularly 50 times compared to GABA<sub>A</sub> receptors subunits containing the  $\alpha_1$ ,  $\alpha_2$  or  $\alpha_3$  subunits. Preferably this binding selectivity is shown over all these subunits.

A preferred class of inverse agonists, which are disclosed in WO-A-9850385, are of formula I:



wherein:

$R^1$  is hydrogen, halogen or CN or a group  $C_{1-4}$ alkyl,  $C_{2-4}$ alkenyl,  $C_{2-4}$ alkynyl,  $C_{1-4}$ alkoxy,  $C_{2-4}$ alkenyloxy or  $C_{2-4}$ alkynyloxy, each of which groups is unsubstituted or substituted with one or two halogen atoms or with a pyridyl or phenyl ring each of which rings may be unsubstituted or  
 5 independently substituted by one or two halogen atoms or nitro, cyano, amino, methyl or  $CF_3$  groups;

$R^2$  is hydrogen, halogen or CN or a group  $C_{1-4}$ alkyl,  $C_{2-4}$ alkenyl,  $C_{2-4}$ alkynyl,  $C_{1-4}$ alkoxy,  $C_{2-4}$ alkenyloxy or  $C_{2-4}$ alkynyloxy each of which groups is unsubstituted or substituted with one or two halogen atoms;

10 L is O, S or  $NR^n$  where  $R^n$  is H,  $C_{1-6}$ alkyl or  $C_{3-6}$ cycloalkyl;

X is a 5-membered heteroaromatic ring containing 1, 2, 3 or 4 heteroatoms independently chosen from oxygen, nitrogen and sulphur, at most one of the heteroatoms being oxygen or sulphur, or a 6-membered heteroaromatic ring containing 1, 2 or 3 nitrogen atoms, the 5- or  
 15 6-membered heteroaromatic ring being optionally fused to a benzene ring and the heteroaromatic ring being optionally substituted by  $R^x$  and/or  $R^y$  and/or  $R^z$ , where  $R^x$  is halogen,  $R^3$ ,  $OR^3$ ,  $OCOR^3$ ,  $NR^4R^5$ ,  $NR^4COR^5$ ,  $tri(C_{1-6}alkyl)silylC_{1-6}alkoxyC_{1-4}alkyl$ , CN or  $R^9$ ,  $R^y$  is halogen,  $R^3$ ,  $OR^3$ ,  $OCOR^3$ ,  $NR^4R^5$ ,  $NR^4COR^5$  or CN and  $R^z$  is  $R^3$ ,  $OR^3$  or  $OCOR^3$ , where  $R^3$  is  
 20  $C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl,  $C_{2-6}$ alkynyl,  $C_{3-6}$ cycloalkyl, hydroxy $C_{1-6}$ alkyl and  $R^3$  is optionally mono, di- or tri-fluorinated,  $R^4$  and  $R^5$  are each independently hydrogen,  $C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl,  $C_{2-6}$ alkynyl,  $C_{3-6}$ cycloalkyl or  $CF_3$  or  $R^4$  and  $R^5$ , together with the nitrogen atom to which they are attached, form a  
 4-7 membered heteroaliphatic ring containing the nitrogen atom as the  
 25 sole heteroatom, and  $R^9$  is benzyl or an aromatic ring containing either 6 atoms, 1, 2 or 3 of which are optionally nitrogen, or 5 atoms, 1, 2 or 3 of which are independently chosen from oxygen, nitrogen and sulphur, at most one of the atoms being oxygen or sulphur, and  $R^9$  is optionally substituted by one, two or three substituents independently chosen from  
 30 halogen atoms and  $C_{1-4}$ alkyl,  $C_{2-4}$ alkenyl,  $C_{2-4}$ alkynyl,  $C_{1-4}$ alkoxy,  $C_{2-4}$ alkenyloxy and  $C_{2-4}$ alkynyloxy groups each of which groups is

unsubstituted or substituted by one, two or three halogen atoms, and when X is a pyridine derivative, the pyridine derivative is optionally in the form of the N-oxide and providing that when X is a tetrazole derivative it is protected by a C<sub>1-4</sub>alkyl group; or X is phenyl optionally substituted by one, two or three groups independently selected from halogen, cyano, C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, C<sub>2-6</sub>alkynyl and C<sub>3-6</sub>cycloalkyl;

Y is optionally branched C<sub>1-4</sub>alkylidene optionally substituted by an oxo group or Y is a group (CH<sub>2</sub>)<sub>j</sub>O wherein the oxygen atom is nearest the group X and j is 2, 3 or 4;

10        Z is a 5-membered heteroaromatic ring containing 1, 2 or 3 heteroatoms independently selected from oxygen, nitrogen and sulphur, at most one of the heteroatoms being oxygen or sulphur and providing that when two of the heteroatoms are nitrogen an oxygen or sulphur atom is also present and that when one of the atoms is oxygen or sulphur then at least one nitrogen atom is present, or a 6-membered heteroaromatic ring containing 2 or 3 nitrogen atoms, Z being optionally substituted by R<sup>v</sup> and/or R<sup>w</sup>, where R<sup>v</sup> is halogen, R<sup>6</sup>, NR<sup>7</sup>R<sup>8</sup>, NR<sup>7</sup>COR<sup>8</sup>, CN, furyl, thienyl, phenyl, benzyl, pyridyl or a 5-membered heteroaromatic ring containing at least one nitrogen atom and optionally 1, 2 or 3 other heteroatoms independently selected from oxygen, nitrogen and sulphur, at most one of the other heteroatoms being oxygen or sulphur and R<sup>w</sup> is R<sup>6</sup> or CN;

R<sup>6</sup> is C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, C<sub>2-6</sub>alkynyl, C<sub>3-6</sub>cycloalkyl, hydroxyC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>2-6</sub>alkenyloxy, C<sub>2-6</sub>alkynyloxy, CH<sub>2</sub>F or CF<sub>3</sub>; and

25        R<sup>7</sup> and R<sup>8</sup> are each independently hydrogen, C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, C<sub>2-6</sub>alkynyl, C<sub>3-6</sub>cycloalkyl or CF<sub>3</sub> or R<sup>7</sup> and R<sup>8</sup>, together with the nitrogen atom to which they are attached, form a 4-7 membered heteroaliphatic ring containing the nitrogen atom as the sole heteroatom;

or a pharmaceutically acceptable salt thereof.

30        As used herein, the expression "C<sub>1-6</sub>alkyl" includes methyl and ethyl groups, and straight-chained and branched propyl, butyl, pentyl and hexyl

groups. Particular alkyl groups are methyl, ethyl, n-propyl, isopropyl and t-butyl. Derived expressions such as "C<sub>1-4</sub>alkyl", "C<sub>2-4</sub>alkenyl", "C<sub>2-6</sub>alkenyl", "hydroxyC<sub>1-6</sub>alkyl", "C<sub>2-4</sub>alkyl" and "C<sub>2-6</sub>alkynyl" are to be construed in an analogous manner.

5           The expression "C<sub>3-6</sub>cycloalkyl" as used herein includes cyclic propyl, butyl, pentyl and hexyl groups such as cyclopropyl and cyclohexyl.

Suitable 5- and 6-membered heteroaromatic rings include pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrrolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, oxadiazolyl and thiadiazolyl  
10           groups. A suitable 5-membered heteroaromatic ring containing four nitrogen atoms is tetrazolyl. Suitable 6-membered heteroaromatic rings containing three nitrogen atoms include 1,2,4-triazine and 1,3,5-triazine.

The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, of which fluorine and chlorine are preferred.

15           As used herein the term "C<sub>1-6</sub>alkoxy" includes methoxy and ethoxy groups, and straight-chained, branched and cyclic propoxy, butoxy, pentoxy and hexoxy groups, including cyclopropylmethoxy. Derived expressions such as "C<sub>2-6</sub>alkenyloxy", "C<sub>2-6</sub>alkynyloxy", "C<sub>1-4</sub>alkoxy", "C<sub>2-4</sub>alkenyloxy" and "C<sub>2-4</sub>alkyloxy" should be construed in an analogous  
20           manner.

Four particular compounds which can be used are:

6-(1-methylimidazol-4-yl)methyloxy-3-(5-methylisoxazol-3-yl)-1,2,4-  
triazolo[3,4-a]phthalazine;  
3-(5-methylisoxazol-3-yl)-6-(1-methyl-1,2,3-triazol-4-yl)methyloxy-1,2,4-  
25           triazolo[3,4-a]phthalazine;  
3-(5-methylisoxazol-3-yl)-6-(2-pyridyl)-1,2,4-triazolo[3,4-a]phthalazine;  
and  
3-(5-methylisoxazol-3-yl)-6-(1-methylimidazol-4-yl)-1,2,4-triazol-3-  
ylmethyloxy-1,2,4-triazolo[3,4-a]phthalazine.

30           The second of the above compounds is particularly favoured.

The present invention also provides a pharmaceutical composition comprising an muscarinic agonist, an inverse agonist of the GABA<sub>A</sub>  $\alpha_5$  receptor subtype and a pharmaceutically acceptable carrier.

There is also provided a kit of parts comprising a first  
5 pharmaceutical composition comprising an muscarinic agonist and a first pharmaceutically acceptable carrier and a second pharmaceutical composition comprising an inverse agonist of the GABA<sub>A</sub>  $\alpha_5$  receptor subtype and a second pharmaceutically acceptable carrier for simultaneous, sequential or separate administration.

10 There is further provided a combination of an muscarinic agonist and an inverse agonist of the GABA<sub>A</sub>  $\alpha_5$  receptor subtype for use in a method of treatment of the human body, particularly for the treatment of a neurodegenerative disorder with associated cognitive deficit such as Alzheimer's Disease or Parkinson's disease, or of a cognitive deficit arising  
15 from a normal process such as aging or of an abnormal process such as injury. The combination is particularly beneficial in the treatment of Alzheimer's Disease.

There is also provided the use of a combination of an muscarinic agonist and an inverse agonist of the GABA<sub>A</sub>  $\alpha_5$  receptor subtype in the  
20 manufacture of a medicament for the treatment of a neurodegenerative disorder such as Alzheimer's Disease or Parkinson's disease, or of a cognitive deficit arising from a normal process such as aging or of an abnormal process such as injury. The treatment of Alzheimer's Disease is particularly preferred.

25 There is also disclosed a method of treatment of a subject suffering from a neurodegenerative disorder, such as Alzheimer's Disease or Parkinson's disease, or a cognitive deficit arising from a normal process such as aging or an abnormal process such as injury, which comprises administering to that subject a therapeutically effective amount of a  
30 combination of an muscarinic agonist and an inverse agonist of the GABA<sub>A</sub>



$\alpha_5$  receptor subtype. The treatment of Alzheimer's Disease is particularly preferred.

The pharmaceutical compositions of the present invention are preferably in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, transdermal patches, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums or surfactants such as sorbitan monooleate, polyethylene glycol, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of each active ingredient of the present invention. Typical unit dosage forms contain from 1 to 100 mg, for example 1, 2, 5, 10, 25, 50 or 100 mg, of each active ingredient. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the

duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

5           The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar  
10       pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

          For the treatment of a neurodegenerative condition, a suitable  
15       dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.01 to 100 mg/kg per day, and especially about 0.01 to 5 mg/kg of body weight per day of each active ingredient. The compounds may be administered on a regimen of 1 to 4 times per day. In some cases, however, dosage outside these limits may be used.

20           The synergistic effect of the combination of the present invention can be shown, for example, by comparing the combined dosage of the combination with dosages of the same amount of each of the active ingredients separately on subjects using the Mini-Mental State Examination (MMSE) as described in Folstein and Folstein J. Psychiat.  
25       Res., 1975, 12, 189-198 or a variant thereof as discussed in Tombaugh and McIntyre, JAGS, 1992, 40, 922-935.

### CLAIMS

1. A combination of an muscarinic agonist and an inverse agonist of  
the GABA<sub>A</sub>  $\alpha_5$  receptor subtype for separate, sequential or simultaneous  
5 administration.
2. A combination according to claim 1 wherein the inverse agonist has  
a functional efficacy at the  $\alpha_5$  receptor subtype of less than 20%, and a  
functional efficacy at the  $\alpha_1$ ,  $\alpha_2$  and  $\alpha_3$  receptor subtypes of between -20  
10 and +20 %.
3. A combination according to claim 1 or 2 wherein the inverse agonist  
has a binding ration of greater than 10:1 to GABA<sub>A</sub> receptors containing  
the  $\alpha_5$  receptor subtype compared to GABA<sub>A</sub> receptors containing the  $\alpha_1$ ,  $\alpha_2$   
15 or  $\alpha_3$  subtypes.
4. A combination according to claim 1 wherein the inverse agonist is  
3-(5-methylisoxazol-3-yl)-6-(1-methyl-1,2,3-triazol-4-yl)methoxy-1,2,4-  
triazolo[3,4-a]phthalazine.  
20
5. A combination according to any one of the preceding claims wherein  
the muscarinic agonist is selected from methacoline and its chloride,  
carbachol, bethanechol, arecholine, pilocarpine, muscarine, McN-A-343,  
oxetremorine, milameline, xanomeline, cis-methyldioxalene, pirenzepine,  
25 gallamine, SB 202026, AF102B, AFDX 116 and RS-86.
6. A pharmaceutical composition comprising a combination as defined  
if any one of claims 1 to 5 and a pharmaceutically acceptable carrier for  
simultaneous administration.

30

7. A kit of parts comprising a first pharmaceutical composition comprising an muscarinic agonist and a first pharmaceutically acceptable carrier and a second pharmaceutical composition comprising an inverse agonist of the GABA<sub>A</sub>  $\alpha_5$  receptor subtype and a second pharmaceutically acceptable carrier for simultaneous, separate or sequential administration.  
5
8. A method of treatment of a subject suffering from a neurodegenerative disorder or a cognitive deficit comprising administering to that subject a therapeutically effective amount of a combination of an  
10 muscarinic agonist and an inverse agonist of the GABA<sub>A</sub>  $\alpha_5$  receptor subtype.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/00801

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K45/06

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 04560 A (MERCK SHARP & DOHME ;REEVE AUSTIN JOHN (GB); STERNFIELD FRANCINE ()) 5 February 1998 (1998-02-05) abstract; claim 8 ---	1-8
A	WO 96 25948 A (MERCK SHARP & DOHME ;DAWSON GERARD RAPHAEL (GB)) 29 August 1996 (1996-08-29) cited in the application abstract; claims ---	1-8
A	WO 92 03433 A (NOVONORDISK AS) 5 March 1992 (1992-03-05) page 1, line 34 - page 2, line 7 --- -/--	1-8



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

### \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
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Date of the actual completion of the international search

24 August 1999

Date of mailing of the international search report

31/08/1999

Name and mailing address of the ISA

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/00801

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 647 580 A (ROSZKOWSKI ADOLPH P) 3 March 1987 (1987-03-03) column 1, line 4,5 column 2, line 4-14 -----	1-8

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 99/00801

### Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
See FURTHER INFORMATION PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

#### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

## Continuation of Box I.2

Present claims relate to an extremely large number of possible combinations. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compositions claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those compounds explicitly mentioned in the claims

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

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